Radiotherapy and Oncology 107 (2013) 134–139

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Radiotherapy with rectangular fields is associated with fewer clinical failures than conformal fields in the high-risk prostate cancer subgroup: Results from a randomized trial

Wilma D. Heemsbergen [a,*], Abrahim Al-Mamgani [b], Marnix G. Witte [a], Marcel van Herk [a], Joos V. Lebesque [a]

[a] Department of Radiation Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam; and [b] Department of Radiation Oncology, Erasmus Medical Center – Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 1 November 2012
Received in revised form 15 March 2013
Accepted 20 March 2013
Available online 3 May 2013

Keywords:
Prostate cancer
High-risk
Subclinical disease
Trial

ABSTRACT

Objective: High-risk prostate cancer patients are at risk for subclinical disease and micro-metastasis at the time of treatment. Nowadays, tight margins reduce dose to periprostatic areas compared to earlier techniques. We investigated whether rectangular fields were associated with fewer failures compared to conformal fields (with lower extraprostatic dose).

Methods: We selected 164 high-risk patients from the trial population of 266 T1-T4N0M0 patients, randomized between rectangular ($n = 79$) and conformal fields ($n = 85$). Prescribed dose was 66 Gy to the prostate and seminal vesicles plus 15 mm margin. We compared clinical failure rates (in- and excluding local failures), between both arms. Dose differences around the prostate were calculated based on an inter-patient mapping method.

Results: Median follow-up was 34 months. There were 9 clinical failures in the rectangular arm versus 24 in the conformal arm ($p = 0.012$). Number of failures outside the prostate was 7 and 19, respectively ($p = 0.025$). We observed average dose differences of 5–35 Gy between the arms in the regions around the prostate.

Conclusions: We found a significantly lower risk of early tumor progression for patients treated with rectangular fields. Treatment failure can probably in part be prevented by irradiation of areas suspected of subclinical disease in high-risk prostate cancer.

Patients treated with radiotherapy for localized prostate cancer have different risk profiles with regard to recurrence of the disease and prostate cancer-related death. Well established predictive factors are: pretreatment Prostate-Specific Antigen (PSA) level, T stage, and Gleason score/differentiation grade. These factors are broadly recognized and used to define low-, intermediate- and high-risk prostate cancer. The definition of Chism et al. [1] identifies low risk as PSA $\leqslant$ 10, T1B-T2a, and Gleason < 7, high-risk as PSA > 20 ug/L, and/or T3, and/or Gleason 8–10, and intermediate risk as all other patients.

High-risk patients show a much higher hazard rate for clinical failures during the first years after radiotherapy compared to low- and intermediate risk. This can be contributed to extracapsular cancer growth into surrounding tissues (e.g. invasion of rectum or bladder neck, perineural invasion), and micro-metastasis to lymph node areas already present at the time of radiotherapy [2–6]. Clinical failures after a longer period of time (e.g. 10 years) can be contributed to local failure of the treatment [2]. Risk estimations of subclinical disease outside the prostate vary from a few percent for low-risk patients to more than 30% for high-risk, depending on the risk profile [6,7].

Elective nodal irradiation in patients with unfavorable prostate cancer is a controversial topic; the presence of micro-metastasis in part of these patients suggests favorable outcomes for elective irradiation, but results from two randomized trials are inconclusive [8,9]. Therefore elective nodal irradiation has remained a point of discussion since the introduction of conformal therapy about 20 years ago [10].

In a previous study we found a dose–effect relationship for accidental dose delivered *outside* the prostate and freedom from failure [11]. This concerned a subgroup of high-risk patients from a randomized trial in which either 68 Gy or 78 Gy was described to the prostate and seminal vesicles with conformal techniques and a 1 cm margin. To validate the results of this explorative analysis, we investigated failure rates of high-risk prostate cancer patients in an independent data set. This concerned data of a previous randomized clinical trial [12] in which the original goal was to look

* Corresponding author. Address: Department of Radiation Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail address: w.heemsbergen@nki.nl (W.D. Heemsbergen).

0167-8140
http://dx.doi.org/10.1016/j.radonc.2013.03.019

into toxicity levels of conformal fields compared to rectangular fields. All patients in this trial were treated with modern three-dimensional (3D) treatment techniques and their setup was monitored and corrected when necessary during treatment. In this toxicity trial patient had been randomized between rectangular fields to treat the prostate and seminal vesicles, and conformal fields (with lower unintended dose to regional areas). Our hypothesis was that rectangular fields may be associated with a lower risk of clinical failure.

Material and methods

Study Population

We reviewed data from a randomized clinical trial performed at the Daniel den Hoed Clinic/Erasmus Medical Center in Rotterdam (The Netherlands). Patient recruitment took place in the period 1994–1996. A total of 266 patients entered this toxicity trial in which adverse toxicity event rates were compared between treatments with conformal fields versus the conventional (at that time) rectangular fields. More details of this study population are described elsewhere [12]. From this patient group, we selected 164 high-risk patients, using criteria described by Chism et al. [1]: PSA > 20 μg/L, or poor differentiation, or T3. Since no Gleason score was available for these patients diagnosed in 1994–1996, we used the differentiation grade to select high-risk patients. Characteristics of the selected high-risk patients are summarized in Table 1. Trial patients with T1B/C tumors were treated for the prostate only and therefore none of them were selected for the current analysis: this excluded 2 high-risk patients with a T1B tumor and poor differentiation.

Treatment

Patients were randomized to either rectangular or conformal radiation fields, stratifying for gross tumor volume. The prescribed dose was 66 Gy in 33 fractions. Patients were instructed to have a full bladder and empty rectum for the planning CT scan. The clinical target volume was the prostate and seminal vesicles plus a 3D expansion of 15 mm. A three-field technique was used with two lateral (oblique) fields and one anterior treatment field which was planned with a 3D planning system (CADPLAN). In the conformal arm, a multi leaf collimator was used to shape the treatment fields. Patient set-up was checked at regular intervals using an electronic portal imaging device. During treatment an Electronic Portal Imaging Device was used to check the patient setup. With "a set-up correction protocol" [13] the average systematic positioning accuracy of the bony anatomy could be limited to 1.5 mm (1 SD) with a average random error of 2.5 mm (1 SD).

Table 1
Patient and treatment data of selected high-risk patients (n = 164).

Characteristics	Rectangular fields (n = 79)	Conformal fields (n = 85)
Mean age in years (1 SD)	70 (6.5)	70 (6.4)
Tumor stage:		
T2A	2	1
T2B	9	7
T2C	22	19
T3A	15	27
T3B	29	22
PSA (μg/L)		
<10	13	15
10–20	19	24
>20	46	45
Unknown	1	1
Differentiation grade		
Good	17	21
Moderate	44	34
Poor	16	25
Unknown	2	5
Neo-adjuvant HT[a]:		
Yes	15	12
No	64	73

[a] HT, hormonal treatment.

Endpoint

No data on follow-up PSA measures or biochemical failure were available for this patient group. Therefore only clinical failure was the study endpoint. Failure could be local, regional, and/or distant metastasis. Procedures to investigate clinical failures were similar in both arms, and were performed according the clinical guidelines: physical exam and blood tests were performed at each follow-up, and if there was an indication for possible tumor progression, additional imaging (like bone scan, CT scan) was performed as decided by the treating physician. The clinical failures in this study were all identified within 3.6 years after treatment. Longer follow-up was not available from this randomized trial since it was designed as a toxicity study.

Dose distributions

We calculated dose maps for each patient, and constructed a dose difference map, by using a mapping procedure which is described by Witte et al. [11]. The dose mapping is based on the prostate contour delineated on the planning CT scan. From one patient to another, two points correspond if their distances to the prostate are equal, and their directions with respect to the center of mass of the prostate are the same. We also evaluated the dose in specific points on the dose map for each individual patient: 3.5 cm and 5 cm from the prostate edge, located in the obturator region. An example of the location of such a point is illustrated in Fig. 1 for two arbitrary patients.

Statistical analysis

We calculated time-to-event curves from the start of RT, using Kaplan Meier estimates. Log-Rank statistic was applied to test differences between groups. A Cox regression model was used to construct a multivariate model. IBM© SPSS© for Windows software was used for the analyses (release 20.0, IBM Corp.).

Results

Tumor progression & survival

Median follow-up was 34 months for patients alive (range 11–48). The number of patients with tumor progression was 9 in the rectangular arm and 24 in the conformal arm (total of 33). The first location of established tumor progression was "local" in 7 cases, "regional" in 2 cases, and "distant metastasis" in 24 cases (Table 2). Kaplan Meier estimates showed a significantly lower risk of the total number of clinical failures for rectangular fields (p = 0.012, Fig. 2). When we count only first failures outside the prostate (excluding first events of local failure), the number of events was 7 and 19, respectively (Log-Rank, p = 0.025). Within the limited follow-up of the study population 24 patients had died (12 in both arms); 6 of them died from prostate cancer (3 in both arms).

Dose differences

Using the dose mapping procedure, we found average dose differences in the range of 5–35 Gy between the arms in the regions

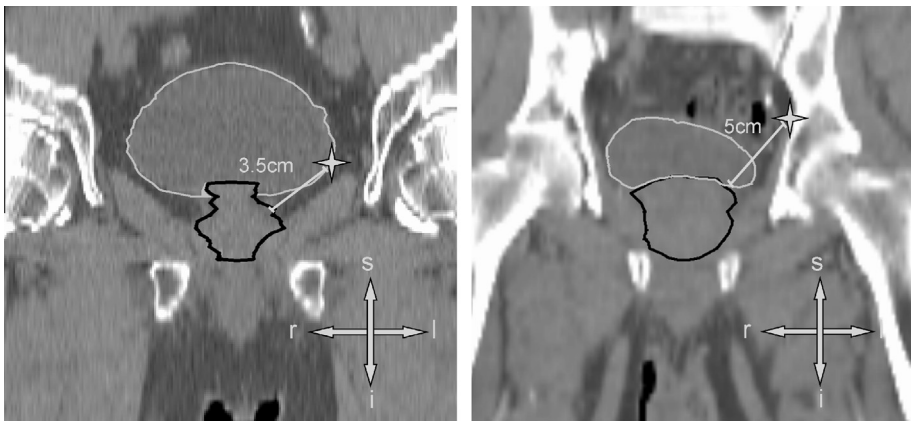

Fig. 1. CT view of two sample patients. The star indicates the position of the two arbitrary chosen points, 3.5 cm (left) and 5 cm (right) from the prostate edge.

Table 2
First failure type.

		First failure type					Total
		NED[a]	Dead NED[a]	Local	Regional	Metastasis	
Treatment field	Rectangular	68	2	2	2	5	79
	Conformal	56	5	5	0	19	85
Total		124	7	7	2	24	164

[a] NED, no evidence of disease.

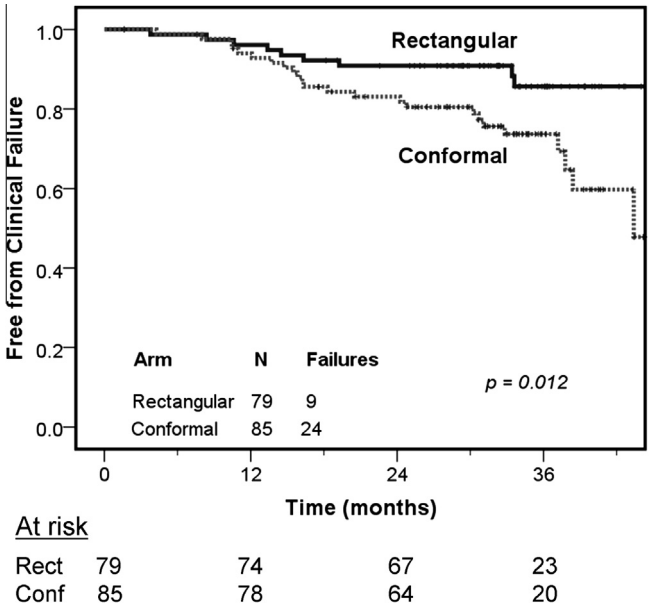

Fig. 2. Freedom from clinical failure for high-risk prostate cancer patients: rectangular arm versus conformal arm.

around the prostate, which is shown in Figs. 3 and 4. In Fig. 3 we plotted isodose difference lines (5, 15, 25 Gy) on a sagittal and coronal CT view of a sample patient. In Fig. 4 the dose distributions in the two chosen points in the region around the prostate are illustrated for each arm separately. The effect of wider margins in the rectangular group is visualized in these histograms. At a distance of 3.5 cm in the obturator region, the median dose was 64.4 Gy in the rectangular arm and 60.2 Gy in the conformal arm. At 5 cm distance, differences are larger: the median dose was 59.4 Gy and 42.0 Gy, respectively (both $p < 0.001$). There are a few patients in the rectangular arm with a relatively low dose 5 cm from the prostate edge: in these cases the delineated seminal vesicles were almost at the same height as the prostate (or lower), in the cranial direction.

Multivariate analysis

We checked the prognostic value of treatment arm in a multivariate Cox regression model with t stage, pretreatment PSA and differentiation grade. Only treatment arm ($p = 0.030$) and differentiation grade ($p < 0.001$) were significant predictors for clinical failure in the MV model.

Discussion

We found significantly fewer clinical failures for high-risk prostate cancer patients treated with rectangular fields, compared to conformal fields. Also the number of failures outside the prostate (excluding local progression) was significantly lower in the rectangular arm. Furthermore, we found relevant and significant dose differences when we compare the dose distributions between the arms: on average higher dose was delivered outside the prostate in the rectangular arm (e.g. in periprostatic tissues, obturatorial and presacral regions). These regions are in close correspondence with the regions indicated in the previous study [11].

The irradiated volumes in this trial are small compared to elective pelvic irradiation fields, and the delivered dose to the lymph node areas in this study is for many cases lower than the optimal dose of at least 46 Gy. The observed gain in tumor control for rectangular fields is probably twofold: firstly, unintended irradiation of lymph node areas is advantageous for a number of patients, and secondly, areas adjacent to the prostate suspect for subclinical disease received a higher dose as well, preventing early failure. For high-risk patients, the numbers of reported cases with tumor cells outside the prostate are high: positive lymph nodes in 64% of Gleason 8–10 (pathological score), 39% of PSA > 20 μg/L, and 37% of pT3 cases [6], but also perineural invasion in 49% [3], bladder neck involvement in 15% of T3 patients [5], extra-capsular extensions

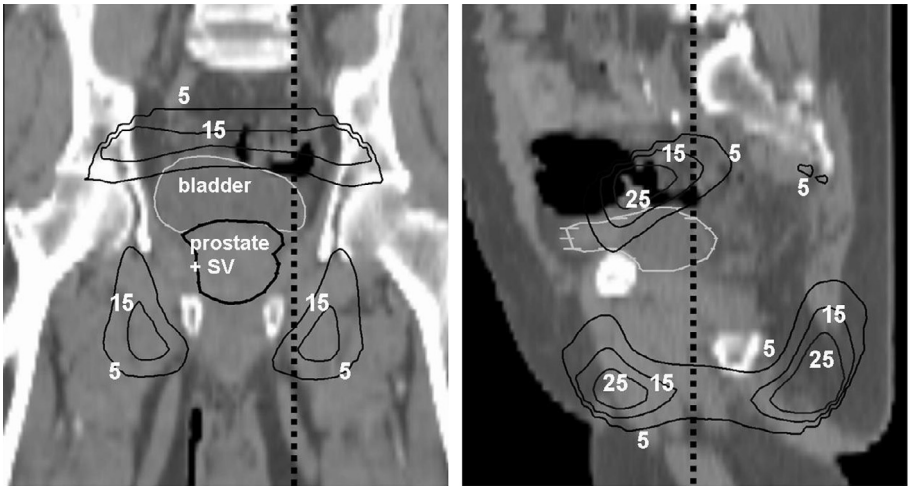

Fig. 3. Dose differences between rectangular and conformal arm (iso dose lines). Coronal (left) plus sagittal (right) CT view of a sample patient. The dotted line indicates the position of the other CT view.

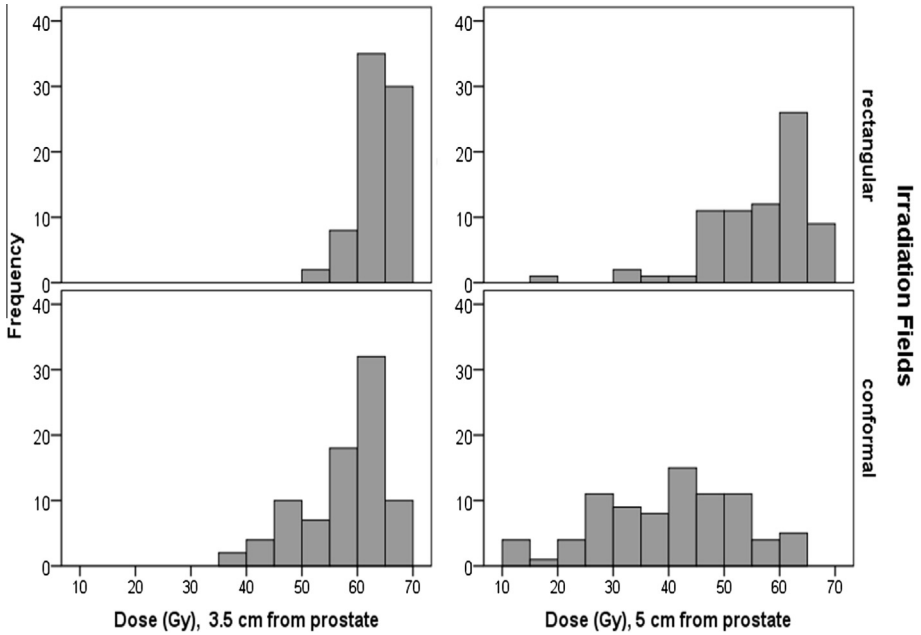

Fig. 4. Histograms of dose in the obturator region within the rectangular and conformal group, 3.5 cm and 5 cm from the prostate edge.

(mainly at rectal site) in 64% of T3 cases [4]. Rectangular fields give higher dose to all of the involved areas and will lower the tumor burden of high-risk cases with extra-prostatic disease and therefore prevent early clinical failures in a number of cases.

When we compare our study population of high-risk patients to the patients treated in the pelvic irradiation trial of Pommier et al., [8], we notice that their trial also treated low- to intermediate risk patients (50% had an estimated nodal involvement <15%). In the RTOG 94–13 trial of Lawton et al. [9], all patients had an estimated nodal involvement of >15% similar to our population, however, their patients were randomized as well to receive neoadjuvant hormonal treatment (NHT) or adjuvant hormonal treatment (AHT). In our study only 16% received NHT or AHT, therefore it is difficult to compare results. Their results were not conclusive about the effect of pelvic RT: they reported a trend of a favorable outcome in patients treated with pelvic fields and NHT compared to the other arms, although the main comparison yielded no significant differences between pelvic fields and prostate only.

In the current trial, patients were treated with modern 3D irradiation techniques, and the treatment included a patient setup correction protocol, limiting the systematic positioning accuracy of the bony anatomy to 1.5 mm (1 SD) with a random error of 2.5 mm (1 SD) [12]. Van Herk et al. [14] showed that with this accuracy 15 mm is a very safe margin. Furthermore, they showed that the total sum of systematic errors (1 SD) has to be larger than 5 mm before the Tumor Control Probability will drop with $\geqslant 1\%$ due to geometric miss of the prostate, and that a 10 mm margin is sufficient to cover for the measured uncertainties in prostate cancer when an offline protocol is used.

Nowadays, prostate markers, cone beam CT, and online setup strategies make it possible to use tighter dose distributions, reducing the unintended dose to areas around the prostate. Margins of about 5–7 mm are applied, and steep dose-gradients are obtained with advanced intensity modulated planning techniques. A number of high-risk prostate cancer patients are, however, likely to develop progression of disease outside the prostate regardless the

local control status. Teh et al. suggested in their study on extracapsular extensions of prostate cancer [4] that planning target volumes should include subclinical disease as well. Several studies report a loss in tumor control in the case of tight margins and distended rectums at planning [15,16], and in one of these studies this loss in tumor control was also observed when prostate markers were used for patient positioning, suggesting geographical miss of (extra-capsular) subclinical disease [16].

Tighter margins and steeper dose-gradients lower the complication probabilities and make it feasible to increase the prescribed dose to the prostate. While this can be expected to increase local control, a decrease in regional control could be the unintended side-effect. One can therefore argue whether higher dose inside the prostate is the best solution for high-risk patients. Our results suggest that high-risk patients may benefit from limited elective irradiation at nodal and/or local extraprostatic areas, to cover for tumor extensions, rectum or bladder involvement and/or (micro) metastasis to lymph nodes. New techniques with intensity modulated radiotherapy have become available for a safe delivery of dose to lymph node areas without unacceptable dose levels to surrounding organs at risk [10,17]. It remains however difficult with the current diagnostic techniques to select the patients that will benefit most from elective irradiation, and to outline the individual relevant elective areas. Since a higher rate of toxicity is only acceptable if the patient is likely to benefit from it by means of prolonged survival, this will probably remain a controversial topic in the near future until improved methods and imaging procedures are available for a more reliable diagnosis concerning identification of micro-metastases and tumor growth in periprostatic tissues.

We evaluated patients treated in another era. Nowadays, hormonal treatment (HT) has become a standard adjuvant treatment in high-risk prostate cancer. Nevertheless, whether dose to periprostatic tissues and nodal areas is needed in (a part of) this high-risk patient population still remains a topical subject. Nowadays, we do not observe many early failures after radiotherapy in high-risk patients because hormonal treatment has become a standard adjuvant treatment. However, subclinical disease outside the prostate at the time of treatment will eventually cause tumor progression once hormonal treatment is completed or when the tumor cells become less sensitive to it [10]. In a previous paper of our group [11] where we reported on a dose–effect relationship for dose outside the prostate in 352 patients treated between 1997 and 2003, 34% of the patients were treated with radiotherapy plus hormonal therapy. The described relationship was seen both in radiotherapy alone patients and in the "radiotherapy plus hormonal therapy" patients.

The dose distribution outside the prostate in this trial looks different from dose distributions in current clinical practice, since the prescribed dose of 66 Gy is low and the applied margins are too generous. However, this data set remains very interesting to evaluate whether there exists a relationship between rectangular fields (with higher dose delivered outside the prostate) and early clinical failure. The question where this subclinical disease is located, and which dose distributions outside the prostate are most optimal for high-risk cases cannot be answered from these data.

The results of the current study should be interpreted carefully since there are some limitations. This trial was not powered and designed for the current study objective. Data on follow-up PSA measurements were not available, and long-term follow-up on survival and prostate cancer related death was not available either. Therefore we were not able to investigate whether this had an impact on prostate cancer specific mortality and overall survival. At the time of study, imaging techniques to identify local and regional failures were less conclusive compared to the techniques nowadays. Therefore we were not able to establish the difference in regional failures rates between the two arms. We find that the data set was however suitable to test our hypothesis from the previous study whether incidental dose outside the prostate is indeed related to tumor progression in high-risk patients. Since it concerned data from a prospective randomized trial, the quality of the data was warranted and therefore interesting to use as an independent data set to test our hypothesis.

Conclusions

In a prior investigation we concluded that incidental dose outside the prostate was associated with failure in high-risk prostate cancer patients treated for the prostate and seminal vesicles only [11]. The current study confirms the findings of that study in an independent patient group with quite different treatment characteristics. The progression of subclinical disease in regions around the prostate can possibly be prevented by limited elective irradiation of lymph node areas and inclusion of subclinical disease in periprostatic tissues. In order to establish which patients would benefit most from such treatment, and which areas should be included, further investigations are needed.

Conflicts of interest

None.

References

[1] Chism DB, Hanlon AL, Horwitz EM, Feigenberg SJ, Pollack A. A comparison of the single and double factor high-risk models for risk assignment of prostate cancer treated with 3D conformal radiotherapy. Int J Radiat Oncol Biol Phys 2004;59:380–5.
[2] Morgan PB, Hanlon AL, Horwitz EM, Buyyounouski MK, Pollack A. Timing of biochemical failure and distant metastatic disease for low-, intermediate- and high-risk prostate cancer after radiotherapy. Cancer 2007;110:68–80.
[3] Feng FY, Qian Y, Stenmark MH, Halverson S, Blas K, Vance S, et al. Perineural invasion predicts increased recurrence, metastasis, and death from prostate cancer following treatment with dose-escalated radiation therapy. Int J Radiat Oncol Biol Phys 2011;81:e361–7.
[4] Teh BS, Bastasch MD, Mai WY, et al. Predictors of extracapsular extension and its radial distance in prostate cancer: Implications for prostate IMRT, brachytherapy and surgery. Cancer J 2003;9:454–60.
[5] Poulos CK, Koch MO, Eble JN, Daggy JK, Cheng L. Bladder neck invasion is an independent predictor of prostate-specific antigen recurrence. Cancer 2004;101:1563–8.
[6] Weckermann D, Dorn R, Trefz M, et al. Sentinel lymph node dissection for prostate cancer: experience with more than 1000 patients. J Urol 2007;177:916–20.
[7] Makarov DV, Trock BJ, Humphreys EB, Mangold LA, Walsh PC, Epstein JI, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. Urology 2007;69:1095–101.
[8] Pommier P, Chabaud S, Lagrange J, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 2007;25:5366–73.
[9] Lawton C, DeSilvio M, Roach M, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94–13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys 2007;69:646–55.
[10] Morikawa LK, Roach M. Pelvic nodal radiotherapy in patients with unfavorable intermediate and high-risk prostate cancer: evidence, rationale, and future directions. Int J Radiat Oncol Biol Phys 2011;80:6–16.
[11] Witte M, Heemsbergen WD, Bohoslavsky R, et al. Relating dose outside the prostate with freedom from failure in the Dutch trial 68 Gy versus 78 Gy. Int J Radiat Oncol Biol Phys 2009;77:131–8.
[12] Koper PC, Janssen P, van Putten W, et al. Gastro-intestinal and genito-urinary morbidity after 3D CRT of prostate cancer: observations of a randomized trial. Radiother Oncol 2004;73:1–9.
[13] Bel A, van Herk M, Bartelink H, Lebesque JV. A verification procedure to improve patient set-up accuracy using portal images. Radiother Oncol 1993;29:253–60.
[14] van Herk M, Remeijer P, Lebesque JV. Inclusion of geometric uncertainties in treatment plan evaluation. Int J Radiat Oncol Biol Phys 2002;52:1407–22.
[15] Heemsbergen WD, Hoogeman MS, Witte MG, Peeters ST, Incrocci L, Lebesque JV. Increased risk of biochemical and clinical failure for prostate patients with a large rectum at radiotherapy planning: results from the Dutch trial of 68 Gy versus 78 Gy. Int J Radiat Oncol Biol Phys 2007;67:1418–24.

[16] Engels B, Soete G, Verellen D, Storme G. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. Int J Radiat Oncol Biol Phys 2009;74:388–91.

[17] Adkison J, McHaffie DR, Bentzen SM, et al. Phase I trial of pelvic nodal dose escalation with hypfractionated IMRT for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:184–90.